Eur J Clin Pharmacol (2012) 68:887–888
DOI 10.1007/s00228-011-1185-2

LETTER TO THE EDITORS

Influence of age, sex, and haplotypes of thiopurine methyltransferase (*TPMT*) gene on 6- mercaptopurine toxicity in children with acute lymphoblastic leukemia

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Received: 27 October 2011 / Accepted: 22 November 2011 / Published online: 14 December 2011
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Dear Editor,

We read with great interest a recent article by Dorababu et al. titled "Epistatic interactions between thiopurine methyltransferase (TPMT) and inosine triphosphate pyrophosphatase (ITPA) variations determine the 6-mercaptopurine toxicity in Indian children with acute lymphoblastic leukemia (ALL)" published in your journal [1]. It is interesting that the authors described the combined influence of *TPMT* and *ITPA* genetic variants on 6-mercaptopurine-induced toxicity using multidimensional reduction analysis. We therefore have a few comments on the following aspects of the article. It is known that TPMT activity is influenced by age and sex in children. Higher activity was observed in male children compared with female children and adults of normal genotype [2]. Age and sex must be considered in evaluating TPMT activity or its adverse effects. The authors adjusted for age and body surface area in multivariate analysis, but sex was not adjusted for. As the study population comprised children of both genders, the investigators might have analyzed age and sex differences in toxicity among different *TPMT* genotypes. The authors used multiple linear regression analysis to predict hematological toxicity and found that 27% of the variability in toxicity could be determined by the genotypes of *TPMT* and *ITPA*. However, the contribution of age, sex, or other demographic characteristics toward toxicity was ignored. The distribution of age and sex, details of ALL types (T or B), relapse status, and risk stratification was not mentioned under different genotype categories in patients receiving MCP-841 protocol. [3]. The reader would be interested to know the impact of genotype on toxicity in specific ALL types.

As the authors of the article sequenced the entire *TPMT* gene, they might consider constructing *TPMT* haplotypes and correlate them with toxicity. This will give an idea about the influence of all variants together. Instead, the authors checked for correlation of genetic variants individually with that of hematological toxicity yielding low coefficients (0.28, 0.3) [4, 5]. Similarly, *ITPA* haplotypes and the interaction of both haplotypes with toxicity may be investigated. It seems that the population has unique haplotypes, and the authors must refer to the report by Jones et al. for haplotype information on *TPMT* [6]. Some genetic variants are not in Hardy–Weinberg equilibrium. This indicates error in genotyping or that samples are from one cluster (mentioned in the discussion section) or might have been associated with clinical parameters or the disease. The authors might investigate this aspect thoroughly so as not to miss any important findings. Further studies in this area must also consider points suggested by us and by the authors.

Conflict of interest The authors declare no conflicts of interest.

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